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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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CARDIORENAL BIOMARKERS AS PREDICTORS OF ADVERSE OUTCOMES IN CARDIOVASCULAR DISEASES: A NARRATIVE REVIEW

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Abstract.

Introduction: In recent years, there has been a growing body of research focused on cardiorenal biomarkers associated with adverse cardiovascular outcomes. This trend reflects the ongoing need to improve diagnostic and prognostic strategies in clinical practice. At the same time, an increasing number of novel biomarkers are being identified, warranting a critical evaluation of their clinical relevance. This review examines current scientific literature addressing the role of the cardiorenal biomarkers Klotho and cystatin C, highlighting their diagnostic and prognostic potential, as well as the prospects for their integration into routine medical care.

Aim: To analyze literature data on potential cardiorenal biomarkers as predictors of adverse clinical outcomes in patients with cardiovascular diseases.

Search Strategy: A literature search was conducted using the scientific databases PubMed, Web of Science, and Google Scholar, as well as electronic scientific libraries eLibrary and CyberLeninka. The search covered a five-year period (2019–2024) and focused on cardiorenal biomarkers as predictors of adverse outcomes in cardiovascular diseases.

Results: This literature review focuses on studies examining cardiorenal biomarkers of adverse cardiovascular outcomes, specifically the proteins Klotho and cystatin C. These biomarkers reflect a range of pathophysiological processes, including myocardial fibrosis, inflammation, endothelial dysfunction, and renal impairment. The analysis of current evidence suggests that the use of such biomarkers enhances the early detection of cardiovascular pathology, facilitates risk stratification, and supports dynamic patient monitoring. Their incorporation into clinical practice is contributing to the development of personalized treatment strategies and improving the precision of diagnostic assessments, ultimately leading to better clinical outcomes.

Conclusions: A review of recent literature on cardiorenal biomarkers associated with adverse cardiovascular outcomes highlights the strong diagnostic and prognostic relevance of Klotho and cystatin C. Reduced levels of Klotho have been linked to both endothelial and renal dysfunction, while cystatin C is recognized as a sensitive indicator of impaired kidney function. Further research is needed to establish standardized thresholds, refine assessment methodologies, and support the integration of these biomarkers into everyday clinical practice.

Key words. Cardiovascular diseases, clinical and laboratory predictors, cardiorenal biomarkers, Klotho protein, cystatin C, prognosis, diagnosis.

Introduction.

Heart failure remains a major and steadily intensifying global health concern, marked by substantial mortality rates and a significant decline in patients' quality of life. Estimates suggest that approximately 64.3 million people worldwide are affected by this condition. Meta-analytical findings indicate that survival rates among individuals with heart failure are 86.5% at one year, 72.6% at two years, 56.7% at five years, and drop to just 34.9% by the tenth year [1]. Since 2002, the incidence of heart failure has risen by nearly 25%, a pattern attributed to demographic aging, improved management of acute coronary syndromes, and the increased prevalence of key risk factors, notably hypertension and atrial fibrillation [2]. Given its high burden and generally unfavorable prognosis, growing efforts are being directed toward identifying more informative biomarkers that can better capture the underlying disease mechanisms and help anticipate clinical deterioration. Contemporary research trends advocate for the use of biomarker panels rather than relying on a single indicator, aiming to improve risk classification and tailor prognostic strategies more precisely [3-5]. A specific area of interest is cardiorenal syndrome (CRS), a complex condition involving reciprocal dysfunction between the cardiovascular and renal systems. As CRS advances, it is often accompanied by compromised organ perfusion, endothelial cell dysfunction, and heightened inflammatory and oxidative responses—all of which contribute to progressive failure of both organs [6-8]. Endothelial cells, forming the inner lining of blood vessels, are vital for regulating vascular tone, immune surveillance, and metabolic exchange. Their impaired function is recognized as a key contributor to the pathophysiology of CRS. In this context, attention has increasingly turned to biomarkers that capture both cardiac and renal impairment. Among the most promising is the α-Klotho protein, which plays an important role in anti-aging pathways and the maintenance of vascular integrity. Reduced α-Klotho expression has been linked to an elevated risk of atherosclerosis, organ dysfunction, pulmonary emphysema, and other degenerative conditions, while higher expression appears to promote longevity and delay disease progression [9,10]. Cystatin C (Cys C), another important biomarker, is a non-glycosylated protein that serves as a sensitive marker of renal filtration. Its blood concentration has also been associated with cardiac remodeling processes, making it a valuable tool for both diagnostic and prognostic applications—particularly in cases of heart failure with preserved ejection fraction (HFpEF) [11]. This article presents a narrative synthesis of recent studies exploring the diagnostic and prognostic roles of Klotho and cystatin C in

the context of heart failure and cardiorenal interactions

Aim. To analyze literature data on potential cardiorenal biomarkers as predictors of adverse clinical outcomes in patients with cardiovascular diseases.

Search Strategy.

The literature search was conducted using the PubMed, Web of Science, Google Scholar, eLibrary, and CyberLeninka databases, covering publications from 2019 to 2024. The search focused on studies examining cardiorenal biomarkers in the context of cardiovascular diseases, with particular attention to the diagnostic and prognostic value of Klotho protein and cystatin C.

Relevant scientific articles were identified using English and Russian keywords, including "cardiovascular diseases," "heart failure," "biomarkers," "Klotho protein," "cystatin C," "cardiovascular prognosis," and "risk stratification."

The review included peer-reviewed full-text publications, as well as data from international clinical guidelines and contemporary statistical reports. Priority was given to studies that discuss the clinical applicability, predictive potential, and mechanistic relevance of the selected biomarkers within cardiovascular pathology.

Ethical Statement:

Our analysis is based on studies previously conducted by other authors; therefore, no ethical committee approval or patient informed consent was required for this review.

Results and Discussion.

Biology of the Klotho Gene:

In 1997, the *klotho* gene was identified as encoding a membrane protein with sequence homology to β-glucosidase enzymes. It was recognized as a key regulator of aging processes, as its reduced expression in mice resulted in a phenotype resembling human aging, characterized by shortened lifespan, infertility, arteriosclerosis, and other age-related pathologies [9]. In humans, the Klotho gene is located on chromosome 13q12 and extends across approximately 50 kilobases, comprising five exons. While its expression is most prominent in renal tissue, the Klotho protein is also found in several other organs, such as the prostate, lungs, liver, skeletal muscles, aorta, pancreas, and brain. The KlB gene, a paralog of Klotho, is located on chromosome 4 and shares a similar genomic organization and overall length with the Klotho gene. Adipose tissue serves as the principal site of β-Klotho expression; nevertheless, its presence has also been identified in various other tissues, such as the lungs, pancreas, aorta and heart. Both genes give rise to protein isoforms that exist in membrane-bound as well as secreted forms [12]. Currently, three isoforms of α-Klotho have been identified: the full-length transmembrane form, a truncated soluble variant, and a secreted version. The full-length isoform of α-Klotho functions as a co-receptor for fibroblast growth factor 23 (FGF23), playing an essential role in regulating phosphate metabolism and maintaining mineral homeostasis [13]. The soluble and secreted isoforms of α-Klotho, collectively known as α-Klotho protein, exert a wide range of physiological effects through both systemic endocrine and local paracrine signaling pathways, influencing various organs such as the kidneys, bones, brain, cardiovascular system, lungs, and vascular endothelium [14-17]. The third member of the Klotho protein family is a transmembrane protein encoded by the Lctl gene. Due to its structural resemblance to lactase, it is commonly referred to as γ-Klotho, KLPH, or LCTL. In humans, this gene is situated on chromosome 15 and displays generally low expression across the majority of tissues, with the highest levels detected in the testes. Among the members of the Klotho protein family, the Klgene demonstrates the highest expression, whereas Lctl exhibits the lowest [18]. α-Klotho and β-Klotho contain two extracellular subdomains (KL1 and KL2), a transmembrane domain, and a cytoplasmic domain, whereas γ-Klotho comprises only a single extracellular KL1 domain. The extracellular domains of Klotho proteins share homology with β-glucosidases but lack the catalytic glutamate residue required for hydrolase activity. The short cytoplasmic domain of Klotho protein is incapable of independent signal transduction, precluding intrinsic receptor activity. Instead, the extracellular domains interact with receptors and ligands, modulating their function in a manner dependent on receptor type and tissue-specific expression levels [19]. Research suggests the ternary complex of FGF23, FGFR1c, and α-Klotho plays a crucial role in regulating calcium and phosphate homeostasis, as well as vitamin D metabolism, by activating the Ras/MAPK signaling pathway in cells expressing Klotho protein. In contrast, in the absence of Klotho protein, FGF2 initiates an alternative signaling cascade via PLCγ, calcineurin, and NFAT [20]. Retrospective studies indicate the potential of α-Klotho as a novel biomarker for the diagnosis of various age-associated conditions, including heart failure, hypertension, diabetes mellitus, and an elevated risk of cardiovascular mortality [21].

Molecular Mechanisms of α-Klotho

In addition, the Klotho protein exhibits notable antioxidative capabilities, promoting the survival of human umbilical vein endothelial cells (HUVECs) under conditions of oxidative stress by upregulating the activity of critical antioxidant enzymes such as superoxide dismutase (SOD), catalase, and heme oxygenase-1 (HO-1), while concurrently suppressing apoptotic pathways. Klotho protein promotes nitric oxide (NO) production and the neutralization of reactive oxygen species (ROS) through activation of the PI3K/Akt signaling cascade and upregulation of the transcription factor Nrf2, a key regulator of cellular antioxidant defense systems [22]. Moreover, circulating α-Klotho is essential for maintaining endothelial function by restoring endothelium-dependent vasodilation, inhibiting apoptotic processes, and enhancing endothelial regeneration, thereby contributing to the preservation of vascular endothelial integrity. By modulating calcium ion (Ca^{2+})-dependent processes through its interaction with TRPC1 and VEGFR-2, α-Klotho reduces vascular permeability. Additionally, it inhibits VEGFR-2 phosphorylation and endocytosis, thereby preventing apoptosis-associated alterations in vascular permeability, downregulation of cadherin expression, and the activation of Ca^{2+}-dependent enzymes, including calpain and caspase-3. Moreover, soluble Klotho protein demonstrates significant anti-inflammatory properties by suppressing NF-κB activation and

attenuating TNF-α-induced expression of adhesion molecules ICAM-1 and VCAM-1 in endothelial cells [23,24]. Thus, α-Klotho exerts a protective effect on the endothelium through its antioxidative and anti-inflammatory properties, as well as its role in the regulation of calcium homeostasis.

Cardiovascular Significance of α-Klotho

In the PEACE trial, which included 3,555 individuals with stable ischemic heart disease and a preserved left ventricular ejection fraction (LVEF >40%), lower circulating concentrations of α-Klotho were found to be independently associated with a greater risk of cardiovascular death and a higher incidence of heart failure–related hospitalizations. This relationship remained statistically robust even after controlling for multiple biomarkers, such as glomerular filtration rate, cystatin C, albumin-to-creatinine ratio, fibroblast growth factor 23 (FGF23), troponin T, NT-proBNP, and C-reactive protein. Moreover, the combination of reduced α-Klotho levels with elevated FGF23 further amplified the risk of mortality or ischemia-related hospitalizations [25]. urthermore, Klotho protein deficiency has been associated with compromised ischemia-induced neovascularization and upregulation of plasminogen activator inhibitor-1 (PAI-1), which collectively contribute to the advancement of fibrotic remodeling, dysfunction of the sinoatrial node, and an increased susceptibility to sudden cardiac death [24]. A study demonstrated that prolonged 20-hour stress exposure increases the incidence of sudden cardiac death, potentially due to impaired conduction or sinoatrial-atrial node blockade. However, the precise molecular and cellular mechanisms underlying this effect remain inadequately defined. It is hypothesized that α-Klotho expression in the sinoatrial node plays a pivotal role in modulating ion channel activity, thereby regulating the excitability of pacemaker cells [26]. Elevated levels of FGF23 and reduced concentrations of α-Klotho have been associated with arrhythmic episodes in patients with paroxysmal or persistent atrial fibrillation [27]. α-Klotho plays a modulatory role in the activity of several plasma membrane ion channels, including sodium/phosphate co-transporters, Na^+/K^+-ATPases, calcium channels, and hERG potassium channels. These channels are essential for maintaining proper cardiac electrical conduction, repolarization processes, and the prevention of abnormal myocardial excitability. These mechanisms underscore α-Klotho as a critical modulator of cardiac function and a potential therapeutic target [19]. α-Klotho deficiency is hypothesized to play a pivotal role in the development of arterial stiffness, a critical factor in the pathogenesis of hypertension. Experimental studies have demonstrated that mice with partial α-Klotho deficiency (Kl+/- genotype) exhibit increased pulse wave velocity, elevated blood pressure, and higher aldosterone levels. Arterial stiffness serves as an early indicator of detrimental structural and functional vascular alterations, substantially increasing the risk of ischemic heart disease and stroke [28-30]. Furthermore, α-Klotho deficiency in aortic smooth muscle cells has been shown to activate autophagy, reduce elastin levels, and upregulate scleraxis expression, thereby promoting the development of arterial stiffness [31]. The physiological manifestations observed in vivo, such as elevated pulse wave velocity and increased blood pressure, are consistent with underlying cellular and molecular alterations. Notably, α-Klotho has been shown to suppress the transcription of CYP11B2, the gene encoding a critical enzyme involved in aldosterone biosynthesis within the adrenal cortex [32]. Furthermore, under conditions of angiotensin II-induced cardiac hypertrophy and fibrosis, Klotho protein has been shown—both in vivo and in vitro—to suppress the expression of fibroblast growth factor 23 (FGF23) in myocardial tissue. Fibroblast growth factor 23 (FGF23), primarily synthesized in bone tissue, plays a key role in maintaining phosphate balance by suppressing its reabsorption in the renal proximal tubules and limiting its overall excretion from the body. A growing body of research indicates that increased circulating levels of FGF23 represent a clinically significant risk factor, linked to higher rates of cardiovascular morbidity and mortality. Elevated levels of FGF23 have been associated with increased left ventricular mass and the onset of hypertrophy, as well as with higher mortality rates among individuals with end-stage renal disease and ischemic heart disease [33]. One of the earliest studies on α-Klotho demonstrated a notable correlation between its circulating levels and both the severity of disease and mortality risk in patients with chronic coronary syndrome (CCS). An analysis of data from 9,871 adults identified a significant correlation between serum α-Klotho levels and the severity of CCS. Lower α-Klotho levels were independently linked to a higher likelihood of chronic coronary syndrome, a 21% increase in all-cause mortality, and a 76% rise in cardiovascular mortality among affected individuals [34]. The molecular mechanisms underlying the pathogenesis of cardiovascular and renal diseases remain a primary focus of scientific inquiry, as understanding protein interactions in pathological processes offers new prospects for therapeutic innovation. The α-Klotho protein, known for its pleiotropic biological actions, is essential for preserving cardiovascular and renal homeostasis. It contributes to the prevention of cardiomyopathy, heart failure, arterial hypertension, and renal impairment. Its participation in cardioprotective and nephroprotective pathways, as well as its regulation at both the serum level and within target cells, is essential for sustaining cellular metabolism and physiological equilibrium. Therefore, α-Klotho represents a promising therapeutic target for both the treatment and prevention of cardiovascular and renal diseases, paving the way for the development of advanced diagnostic and therapeutic strategies.

Cystatin C.

Renal Function Assessment Using Cystatin C:

Cystatin C is a low-molecular-weight protein (13 kDa) produced by all nucleated cells in the human body. It is freely filtered through the glomeruli and is subsequently fully metabolized within the proximal renal tubules [35]. Cystatin C is employed as a biomarker for estimating glomerular filtration rate (GFR), analogous to serum creatinine. However, its levels are considered less susceptible to external factors such as age, sex, or muscle mass, thereby providing a more reliable assessment of renal function [36]. The definition and staging of chronic kidney disease (CKD) are of paramount importance for risk stratification, as CKD is strongly associated with an

elevated risk of cardiovascular disease (CVD), end-stage renal disease (ESRD), and overall mortality [37]. A meta-analysis of 11 studies comprising over 90,000 participants reported that the prevalence of an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m² was 10% when determined using serum creatinine (sCr), compared to 14% when assessed with cystatin C (CysC) [29]. Among individuals with an eGFRcr of 60–89 mL/min/1.73 m², CysC reclassified 14% into the <60 mL/min/1.73 m² category. Furthermore, in patients with an eGFRcr of 45–59 mL/min/1.73 m², CysC reclassified 42% into lower and 24% into higher eGFR categories, underscoring its potential for refining renal function assessment. Moreover, when estimated GFR was recalculated using cystatin C (eGFRcys), leading to a reclassification to a milder stage of chronic kidney disease compared to creatinine-based estimates (eGFRcr), this shift was linked to a lower risk of progressing to end-stage renal disease (ESRD). Conversely, the reclassification of eGFRcys to a more advanced CKD stage was linked to an increased risk of ESRD progression [38,39]. In the REGARDS study, which evaluated data from 26,643 adults across the United States, individuals who were reclassified to a more severe stage of chronic kidney disease based on cystatin C–estimated GFR (eGFRcys) demonstrated a fourfold higher risk of progressing to end-stage renal disease compared to those reclassified to a less advanced stage [40]. Within the framework of the Cardiovascular Health Study, a decline in eGFR below 60 mL/min/1.73 m² was associated with an increased risk of end-stage renal disease, but only when this reduction was confirmed using cystatin C–based estimates [41]. Over the past 20 years, multiple large-scale studies and meta-analyses involving populations with and without chronic kidney disease (CKD) have consistently shown that cystatin C (CysC) has a stronger and more linear relationship with both all-cause mortality and cardiovascular disease risk than serum creatinine (sCr) [38,40,42-45]. In a 2017 study conducted by Opotowsky et al., it was found that in patients with Fontan circulation, the glomerular filtration rate (GFR) estimated using cystatin C was significantly lower than that of healthy individuals (114.2 ± 22.8 vs. 136.3 ± 12.8 mL/min/1.73 m²; $p < 0.0001$). A higher cystatin C-based GFR was associated with a lower risk of adverse events (HR per 1 SD = 0.66; 95% CI: 0.48–0.90), whereas creatinine-based GFR did not demonstrate a similar association. The authors concluded that cystatin C serves as a more informative prognostic marker in this patient population [46].

Cardiovascular and Prognostic Value of Cystatin C

A recent study demonstrated that the sarcopenia index (SI), derived from the creatinine-to-cystatin C ratio, is an independent factor associated with heart failure with preserved ejection fraction (HFpEF). Furthermore, a diagnostic model incorporating SI exhibited high accuracy and clinical relevance. Given that sarcopenia is a common comorbidity in heart failure, including HFpEF, and adversely impacts physical function and patient prognosis, its assessment may offer valuable insights for risk stratification and clinical management [47]. A study further demonstrated a significant correlation between serum homocysteine (Hcy) and cystatin C (CysC) levels and key clinical parameters, including cardiac function, ventricular remodeling, and overall prognosis in patients with heart failure with preserved ejection fraction (HFpEF). Patients with elevated levels of these biomarkers exhibited compromised cardiac function, more pronounced alterations in left ventricular geometry—as indicated by increased left ventricular end-diastolic diameter (LVEDD), end-systolic diameter (LVESD), and left ventricular mass index (LVMI)—as well as a greater risk of unfavorable cardiovascular outcomes [11]. Moreover, a study demonstrated that the prevalence and progression of chronic kidney disease (CKD) increase with advancing age, with estimates varying depending on the filtration marker utilized. Creatinine-based eGFR (eGFRcr) yielded the lowest CKD prevalence rates, whereas cystatin C-based eGFR (eGFRcys) more frequently identified CKD, particularly in older age groups. The progression of CKD was least pronounced when assessed using eGFRcr (9%) and most pronounced with eGFRcys (18%), underscoring the influence of filtration marker selection on disease classification and longitudinal monitoring [48]. Thus, cystatin C (CysC) is an invaluable and precise marker of renal function, increasingly integrated into clinical practice due to its ability to minimize the influence of factors such as age, sex, and muscle mass. It provides a more reliable estimation of glomerular filtration rate (GFR) compared to creatinine, particularly in elderly patients and complex clinical scenarios. The utility of CysC extends beyond the diagnosis and classification of chronic kidney disease (CKD), encompassing applications such as renal function monitoring, cardiovascular risk prediction, and the optimization of clinical decision-making. The expanded implementation of CysC across diverse clinical settings enhances diagnostic accuracy and contributes to more effective management of patients with kidney disease and associated comorbidities, paving the way for advancements in personalized medicine.

Conclusion.

The biomarkers α-Klotho protein and cystatin C exhibit high diagnostic and prognostic value in assessing cardiovascular and renal risk. α-Klotho protein plays a pivotal role in cardiovascular and renal protection by regulating metabolic and antioxidative processes, positioning it as a potential therapeutic target. Cystatin C, a highly accurate marker of renal function, surpasses creatinine in estimating glomerular filtration rate and holds significance not only in the diagnosis of chronic kidney disease but also in the prediction of cardiovascular complications. Further research is essential to standardize the clinical implementation of these biomarkers and optimize their utility in routine medical practice.

Conflict of interest.

The authors declare that there is no conflict of interest, and that no part of this article has been published in the open press and is not under consideration by other publishers.

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